However, contained herein are amendments to the pending claims that should place the application in condition for allowance.

Objection under 35 U.S.C. §132

> Whenever, on examination, any claim for a patent is rejected, or any objection or requirement made, the Director shall notify the applicant thereof, stating the reasons for such rejection, or objection or requirement together with such information and references as may be useful in judging of the propriety of continuing the prosecution of his application; and if after receiving such notice, the applicant persists in his claim for a patent, with or without amendments, the application shall be reexamined. No amendment shall introduce new matter into the disclosure of the invention.

On page 2, section 6 the USPTO objected to the amendment filed on June 11, 1998, because it allegedly introduced new matter into the disclosure. The Examiner stated that claim 70 allegedly introduced new matter into the disclosure of the invention. Specifically, the Examiner purports that "[t]he disclosure as originally filed does not teach these specific nucleotide fragments."

Claim 35, as originally filed, claims "[p]rotein according to one or more of the preceding claims, characterized in that said protein comprises at least those amino acids which are encoded by nucleotides 74-154 or 155-685." *See* Specification as filed, page 42, lines 11-15. It is well known that an applicant "may rely not only on the description and drawing as filed but also on the original claims if their content justifies it." *See* M.P.E.P. § 608.01(l).

Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to the June 11, 1998 Amendment under 35 U.S.C. §132. Applicants respectfully traverse this objection.

Rejections under 35 U.S.C. § 112 ¶ 2

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

On page 2, section 5 the USPTO rejected claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. § 112 ¶ 2, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards

as the invention. Specifically, the Examiner purports that the word "optionally", recited in claims 36 and 72, "does not clearly describe the claimed subject matter since it cannot be determined if the claims include the limitations following the word 'optionally'."

Applicants have amended claims 36 and 72 accordingly, and believe that the Examiner's concerns have been addressed.

The Examiner rejected claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. § 112 ¶ 2, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner purports that through the use of the claim language "a partial amino acid sequence encoded by the DNA hybridizing to the cDNA," recited in claims 41 and 47, "[i]t is unclear if this partial amino acid sequence is completely encoded by the hybridizing DNA or if the hybridizing DNA consists of a fragment of the coding sequence."

Applicants have amended claim 41 accordingly, and believe that the Examiner's concerns have been addressed.

Applicants respectfully request clarification as to the rejection of claim 47 for the reasons stated above. Based on Applicant's records, claim 47 lacks any hybridization language. Applicants respectfully request that the Examiner indicate if the PTO records reflect otherwise.

Rejections under 35 U.S.C. § 101

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

On page 3, the USPTO rejected claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. §101 as allegedly not supported by either a specific, substantial asserted utility or a well established utility. More specifically, the Examiner purports that "the specification fails to provide any objective evidence that the claimed protein can differentiate untransformed human leukemia cells *ex vivo*." In addition, the Examiner asserts that "there are no teachings in the specification regarding how to use erythroid cells which have not extruded nuclei to become erythrocytes."

The burden that must be met to satisfy the utility requirement of 35 U.S.C. § 101 is not overwhelming. The Federal Circuit has recently supported this rationale by stating that, "[t]he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." Juicy Whip v. Orange Bang, 185 F.3d 1364, 1366 (Fed. Cir. 1999) (quoting Brenner v. Manson, 383 U.S. 519, 534 (1966); emphasis added). The claimed protein has an readily identifiable benefit (i.e., inducing the differentiation of leukemia cells), consistent with the threshold requirement of 35 U.S.C. §101.

The Examiner asserts that the specification "essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed protein." Applicants respectfully disagree. The specification provides at least one use that is both specific and substantial.

In order to satisfy the requirements of 35 U.S.C. §101, Applicants must provide a utility that is both specific (to the subject matter claimed) and substantial (e.g., a real world use). *See* M.P.E.P. § 2107.01(I). Applicants have provided numerous utilities in the specification that are both specific and substantial. The specification, for example, discloses that the protein of the invention shows differentiation-inducing activity "for murine Friend virus-transformed erythroleukemia cell lines *as well as for a human leukemia cell line*." *See* Specification, Page 6, lines 22-25 (emphasis added). As one of skill in the art would understand, the ability to induce differentiation of leukemia cell lines will result in the terminal differentiation of some leukemia cells leading to the erythropoiesis and the formation of erythrocytes. Such activity, by its very nature, serves the dual functions of providing an alternate approach to existing cancer therapy, as well as the induction of "the formation of red blood cells in bone marrow and/or lymphopoietic tissue...impaired owing to illness or treatment," irrespective of whether the cells are infected or transformed by virus. *See* Specification, Page 9, lines 29-32.

Accordingly, there is at least one stated utility for the claimed protein that is both specific (i.e., not all proteins induce the differentiation of leukemia cells) and substantial (i.e., therapeutic methods for treating disease are real world uses), as well as credible. "[A] disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a particular therapeutic application of the compound does contain an assertion of specific and substantial utility for the invention." *See* M.P.E.P. § 2107.02(II)(A).

Furthermore, "pharmacological or therapeutic inventions that provide any 'immediate benefit to the public' satisfy 35 U.S.C. § 101." *See* M.P.E.P. § 2107.01(III) (emphasis in original).

Applicants have satisfied the requirements of 35 U.S.C. § 101 by providing at least one utility which is both specific and substantial. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. § 101 as allegedly not supported by either a specific, substantial asserted utility or a well established utility.

Applicants respectfully traverse this rejection.

Rejections under 35 U.S.C. § 112 ¶ 1

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

On page 4, section 9, the USPTO rejected claims 36-39, 41-42, 45-47, 62, 66-67, and 69-72 under 35 U.S.C. §112 ¶ 1, as allegedly "not supported by either a asserted utility or a well established utility for the reasons set forth above."

As stated in the 35 U.S.C. §101 rejection discussion, Applicants have provided a utility that is both specific and substantial, as well as credible. PTO guidelines state that, "[o]ffice personnel should not impose a 35 U.S.C. §112 ¶ 1, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper." See M.P.E.P. §2107.01(IV). Because Applicants have asserted a utility for the claimed invention that satisfies the requirements of 35 U.S.C. §101, rejection of the same claims under 35 U.S.C. §112 ¶ 1, as lacking utility is not proper.

Applicants respectfully traverse this rejection.

On page 4, section 10 claims 36-39, 41, 42, 45-47, 62, 66, 67 and 69-72 were rejected as not enabled under 35 U.S.C. §112 ¶ 1.

The United States Patent Office purports the specification is only enabled for claims limited to polynucleotides that encode "SEQ ID NO:3 and 5, degenerate coding sequences thereof and the polynucleotides comprising SEQ ID NO:1, 2, 4 and 6-10 and the complete complements of said polynucleotides, because the specification does not reasonably provide enablement for polynucleotides that

encode for fragments of SEQ ID NO: 3 and 5, amino acid fragments of SEQ ID NO: 3 and 5, or polynucleotide variants or fragments of SEQ ID NO: 1, 2, 4, and 6-10." More specifically, the USPTO purports that the "specification has not taught how to make proteins comprising fragments of the disclosed differentiation inducing factor that retain the function of the original SEQ ID NO: 3 or 5 and further, the specification has not shown that polynucleotides encoding polypeptide variants of the disclosed differentiation inducing factor are capable of functioning..."

As is notoriously well established under 35 U.S.C. §112 ¶ 1, "the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (*United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1986)). The factors to be considered in determining whether a disclosure would require undue experimentation include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 773 (1988). In the present case, a person skilled in the art could readily ascertain other proteins possessing the activity of the invention, and test said proteins or fragments thereof according to the methods provided.

The USPTO further purports that the specification "gives no guidance on or exemplification of how to make the polynucleotides that encode the broadly claimed polypeptides." The applicant on pages 18-22 provides a comprehensive disclosure describing the physical and functional properties of the protein, preferred tissues to obtain sequences and fragments thereof, and methods of testing sequences and fragments for erythroid differentiation activity. The applicant notes by way of example only that the specification at least on pages 2 lines 24-28 and page 3 lines 1-4, discusses the gene as "expressed in the form of different RNA species (presumably splice variants) of about 800, 1,200, 1,350, 1,750, and 2,200 bp" as exemplification of possible fragments. In *Ex parte Mark*, the Board of Patent Appeals particularly addressed the breadth of claims under 35 U.S.C. §112 ¶ 1 for protein sequences stating "...one skilled in the art would be able to routinely determine whether deletion or replacement of cysteine residues would result in a mutein which is within the claims." 12 U.S.P.Q.2d 1904, 1907 (1989) Furthermore,

similar to the present application, the Board recognized that "[o]ne skilled in the art is clearly able to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity." 12 U.S.P.Q.2d 1904, 1907 (1989)

With respect to the enablement of fragments, the issue is a rather straight forward one: would a person skilled in the art in possession of the full length sequence be able to (1) make fragments of the segments and (2) determine when such fragments have the desired activity? The answer here is a resounding yes! More particularly it is now recognized routine practice for one skilled in the art to obtain a large sequence and utilize routine practices to obtain active fragments thereof. The court in *Ajinomoto Co. Inc.*, recognized that "how to identify ...genes...in the donor bacterium, how to obtain a chromosome DNA fragment, how to obtain suitable plasmids, how to isolate recipient bacterial strains, and how to perform transformation steps" are "well known to those skilled in the art." 56 U.S.P.Q.2d 1332, 1345 (Fed. Cir. 2000).

The USPTO cites articles by Burgess et al. and Lazar et al. as examples of how unpredictable protein chemistry is in the area of biotechnology, purporting that these reference demonstrate "that even a single amino acid substitution" may dramatically effect biological activity and protein characteristics which would require undue experimentation to practice the claimed invention. Here, however, the disclosure provides one skilled in the art routine methods of identifying and testing which fragments of the claimed sequences induce differentiation according to the specification on pages 18-22. Furthermore, *Ex parte Mark*, makes clear that the ability to start with disclosed fragments and perform testing by a known method is sufficient under 35 U.S.C. §112 ¶ 1. 12 U.S.P.Q.2d 1904 (1989)

The examiner is improperly restricting the applicant to their examples. As the court *In re Angstadt* stated, "[t]o require such a complete disclosure would apparently necessitate a patent application or applications with 'thousands' of examples or the disclosure of 'thousands' of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides." "More importantly, such a requirement would force an inventor to carry out a prohibitive number of actual experiments." 537 F.2d 498, 502 (1976). The applicant provides by way of example several sequences and methods for

testing said sequences for erythroid differentiation activity and should not improperly limited to the examples.

Applicants respectfully traverse this rejection.

Rejections under 35 U.S.C. § 102

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

On pages 5-6, section 11 of the Office Action the USPTO rejected claims 36-39, 45-46, 66, and 69-72 under 35 U.S.C. § 102(b) as allegedly anticipated by Dormer et al (Experimental Hematology, 1992, Vol. 20, p. 758).

A claim may be barred under 35 U.S.C. § 102(b) if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States." *See* M.P.E.P. § 2133. Claims 36-39, 45-46, 66, and 69-72 claim polypeptide sequences encoded by polynucleotide sequences corresponding to SEQ ID NOs: 2 and 6-10. As aptly noted by the Examiner, Dormer et al. do not disclose the polynucleotide sequences of SEQ ID NOs: 2 and 6-10. Therefore, Dormer et al. is not available as proper 35 U.S.C. § 102(b) art against claims 36-39, 45-46, 66, and 69-72.

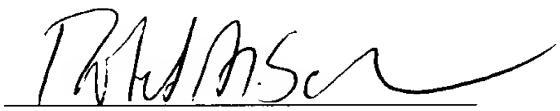
Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 36-39, 45-46, 66, and 69-72 under 35 U.S.C. § 102(b).

Applicants respectfully traverse this rejection.

Conclusion

Applicants believe that incorporation of the amendments and consideration of the above remarks have placed this application in a condition for allowance. Early notification of a favorable consideration is requested.

Respectfully submitted,



Robert M. Schulman
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Attachment A

36. (Thrice Amended) An isolated protein with differentiation-inducing activity on Friend Erythroleukemia cell lines comprising the following properties:

induces differentiation in Friend Erythroleukemia cell lines with hemoglobin formation;

a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran;

~~optionally~~ with an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

is encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7;

with corresponding mRNA species of different length comprising identical 3' regions corresponding to the coding region of SEQ ID NO:2, but different 5' regions.

41. (Twice Amended) Protein according to claim 36, wherein said protein comprises a partial amino acid sequence encoded by a DNA hybridizing to a fragment of the cDNA or SEQ ID NO:1 or NO:2 or NO:4 under stringent conditions.

72. (Thrice Amended) An isolated protein with differentiation-inducing activity on Friend erythroleukemia cell lines comprising the following properties:

induces differentiation in Friend erythroleukemia cell lines with hemoglobin formation;

a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran;

~~optionally~~ with an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

is encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7 or sequences which hybridize with said repeat sequences under stringent conditions;

with corresponding mRNA species of different length comprising identical 3' regions corresponding to the coding region of SEQ ID NO:2 or sequences which hybridize with said coding region under stringent conditions, but different 5' regions, said stringent conditions comprising hybridization at 65°C in an aqueous solution or at 42°C in 50% formamide and subsequent washing of the filter at 60°C in an

aqueous solution having a salt concentration of 15mM NaCl and a concentration of SDS of 0.1%.

Attachment B

36. (Thrice Amended) An isolated protein with differentiation-inducing activity on Friend Erythroleukemia cell lines comprising the following properties:

induces differentiation in Friend Erythroleukemia cell lines with hemoglobin formation;

a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran;

with an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

is encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7;

with corresponding mRNA species of different length comprising identical 3' regions corresponding to the coding region of SEQ ID NO:2, but different 5' regions.

41. (Twice Amended) Protein according to claim 36, wherein said protein comprises a partial amino acid sequence encoded by a DNA hybridizing to a fragment of the cDNA or SEQ ID NO:1 or NO:2 or NO:4 under stringent conditions.

72. (Thrice Amended) An isolated protein with differentiation-inducing activity on Friend erythroleukemia cell lines comprising the following properties:

induces differentiation in Friend erythroleukemia cell lines with hemoglobin formation;

a molecular weight in the range of about 10-60 kDa as determined by gel filtration on a cross-linked allyl dextran;

with an expression of the corresponding mRNA in primary cells of the thymus, fetal liver, adult spleen, or bone marrow;

is encoded by a cDNA comprising repeat sequences of SEQ ID NOS: 6 and 7 or sequences which hybridize with said repeat sequences under stringent conditions;

with corresponding mRNA species of different length comprising identical 3' regions corresponding to the coding region of SEQ ID NO:2 or sequences which hybridize with said coding region under stringent conditions, but different 5' regions, said stringent conditions comprising hybridization at 65°C in an aqueous solution or at 42°C in 50% formamide and subsequent washing of the filter at 60°C in an

aqueous solution having a salt concentration of 15mM NaCl and a concentration of SDS of 0.1%.